UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,722	09/26/2005	Dan Smith	8114-009-WO-US	5983

32301 7590 09/26/2007

CATALYST LAW GROUP, APC
9710 SCRANTON ROAD, SUITE S-170
SAN DIEGO, CA 92121

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
09/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,722	SMITH ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6-27-07, 2-13-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 9-26-05.

Claims 1-37 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of inducing apoptosis or cell death in transformed or non-transformed cells in vitro and in vivo comprising the administration of RNA strands.

The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising this broad array of RNA strands, which, upon administration in vitro or in vivo, provide for apoptosis or the death of transformed and untransformed cells.

The specification discloses the differential apoptotic or cell killing effects of size fractionated synthetic RNAs, where pApU and pA provide for either high or low target

cell killing effects, depending on their cursory size fractionation. The genus of compounds claimed, however, encompasses a broad array of structures, whereby any RNA strands, double stranded or single-stranded, of any sequence, provide for cell killing or apoptotic effects in vitro or in vivo. The specification and claims do not adequately teach a representative number of species for the broad genus claimed. Concise structural features that could distinguish structures within the genus from others are missing from the disclosure, whereby a representative number of species is particularly described which provides for the functions claimed, of providing apoptotic or cell killing effects in transformed and non-transformed cells. For these reasons, the instant disclosure fails to provide adequate written description for the broad genus claimed.

Claims 1-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method of inducing apoptosis or cell death in a subset of transformed target cells comprising the administration of fractionated pApU and pA, does not reasonably provide enablement for the ability to induce apoptosis or cell death in transformed or non-transformed cells in a patient comprising the administration of any RNA strands of any size and any sequence.

The claims are drawn to methods of inducing apoptosis or cell death in transformed or non-transformed cells in vitro and in vivo comprising the administration of RNA strands.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of nucleic acid treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo success. (A. Branch, Trends in Biochem. Sci. 23: 45-50; *see* entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using nucleic acid based approaches. Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of nucleic acids in sufficient amounts to effect a phenotype or desired effect in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic nucleic acids to target cells).

See also the discussion by Opalinska et al of unpredictability of nucleic acid therapy, including the use of siRNA and antisense in vivo (Opalinska et al, Nature Rev., 1: 503-514, at 503 and 511). "Although conceptually elegant, the prospect of using nucleic-acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain... The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field. ...it is widely appreciated that the ability of nucleic-acid molecules

to modify gene expression in vivo is quite variable, and therefore wanting in terms of reliability." [references omitted].

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inducing apoptosis or cell death in transformed or non-transformed cells in vitro and in vivo comprising the administration of RNA strands. The specification teaches differential apoptotic or cell killing effects of size fractionated synthetic RNAs, where whole pApU, whole pA provide for either high or low target cell effects, depending on their size fractionation. These teachings, however, are not representative of the ability to predictably deliver adequate quantities of any RNA strands of any sequence to transformed and non-transformed cells in a subject, whereby apoptosis and/or cell death in induced in any transformed or untranformed target cell upon administration of any RNA of any size and sequence. The specification as filed fails to provide the requisite, particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and the subsequent induction of cell death of any target cell in vitro and in vivo upon administration of the broad genus of compounds claimed.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to methods of inducing apoptosis or cell death in transformed or non-transformed cells in vitro and in vivo comprising the administration of RNA strands of any size and any sequence. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites,

modes of delivery and formulations to target appropriate cells and /or tissues whereby cell death or apoptosis is induced in a subject upon the administration by any means of any RNA strands of any size and sequence. Since the specification fails to provide sufficient guidance for the successful induction of cell death and/or apoptosis in vivo of a representative number of RNA strands, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7,11-13, 16-21, 24-30 and 32-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Lau et al (USPN 5,976,800).

Lau et al (USPN 5,976,800) teach compositions and methods of inducing apoptosis or cell death in transformed cells in vitro and in vivo comprising the administration of ss and dsRNA strands between 1kDA and 50kDa, at a dosage between 1-500 ug/kg (see especially the abstract, col. 2-4; col. 11-12; col. 20-23).

Claims 11-13, 16, 18, 21, 24-26, 28-30 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Romero et al (J. Biol. Chem., Vol. 273, No. 13, pages 7776-7781 (1998)). Romero et al teach compositions and methods of inducing

apoptosis or cell death in transformed and non-transformed cells in vitro comprising the administration of ss and dsRNA strands (pU) between 1kDA and 50kDa (see the abstract on p. 7776; bridging paragraph, pp. 7776-7; second full paragraph on p. 7781).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
9-21-07

TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER